INTRODUCTION
Diabetes mellitus (DM) is a disease characterized by hyperglycemia or a condition in which glucose in the blood increases or exceeds normal limits, which occurs due to the pancreas’s deficiency or decreased effectiveness of insulin. According to the International Diabetes Federation (IDF), in 2015, the incidence of diabetes mellitus in the world was 415 million people, where the proportion of the incidence of type 2 diabetes mellitus was 95% of the world’s population suffering from diabetes. It was also stated that Indonesia was ranked seventh globally, with an estimated number of people with DM as many as 10 million people. It is estimated that by 2040, the number will increase to 16.2 million. DM is ranked fourth in chronic disease in Indonesia based on its prevalence. Riskesdas data in 2013 stated that the national prevalence of DM was 6.9%. Referring to the national prevalence, DKI Jakarta has a total prevalence of DM of as much as 2.5%, where DKI Jakarta is ranked 2nd out of 33 provinces in Indonesia. Many sufferers are in the age range of 56-64 years, with a prevalence of 4.8%. The increasing prevalence of DM requires the Indonesian government always to handle and treat DM patients.

According to Perkeni (Indonesian Endocrinology Association), handling cases of type 2 DM consists of 4 pillars, namely: (1) education; (2) meal planning (diabetic diet); (3) physical exercise or exercise; and (4) pharmacological intervention which may consist of administering oral antidiabetic drugs (OAD) alone or in combination and administration of insulin. Pharmacological intervention is given if blood glucose has not decreased only by changing lifestyle. Patients with type 2 diabetes can be given OAD drugs such as Sulfonylureas, Glinids, Biguanides, Thiazolidinediones (TZD), and alpha-glucosidase inhibitors DPP-IV and SGLT-2. Administration can be done singly or in combination early on by looking at the patient’s clinical condition and starting with a low dose.

The effectiveness of OAD drugs given alone and in combination to patients for lowering blood glucose is not yet known clearly because they often differ depending on the patient’s condition. Based on this description, it is necessary to compare the effectiveness of oral antidiabetic drugs. Therefore, researchers are encouraged to conduct this study to compare the effectiveness of a single oral antidiabetic drug with a combination in patients with diabetes mellitus at the Indonesian Christian University General Hospital from January 2014 to July 2017. Combined oral antidiabetic drugs are more effective than single oral antidiabetic drugs in lowering blood sugar in type 2 diabetes mellitus.
LITERATURE REVIEW

Diabetes mellitus (DM) is a group of glucose metabolic diseases characterized by hyperglycemia due to defects in insulin secretion, insulin action or both 4. This chronic metabolic disease is caused by the pancreas not producing enough insulin or the body not using the insulin it produces effectively. Insulin is a hormone that regulates the balance of blood sugar levels, increasing the concentration of glucose in the blood (hyperglycemia). Type 1 diabetes mellitus, also known as IDDM, is a glucose metabolic disease caused by damage to the beta cells of the islets of Langerhans in the pancreas. The damage that occurs can be caused by an autoimmune reaction that destroys the islets of Langerhans beta cells so that the amount of insulin produced is reduced or even stopped. Apart from autoimmunity, some causes of IDDM have no known aetiology (idiopathic) 5.

Type 2 diabetes mellitus is a metabolic disease characterized by hyperglycemia due to the insensitivity of cells to insulin due to impaired insulin function (insulin resistance) and decreased insulin secretion. Type 2 diabetes mellitus is also referred to as non-insulin-dependent diabetes mellitus (NIDDM) because the beta Langerhans cells of the pancreas still produce insulin even though they have decreased 6. Several factors are known to influence the occurrence of diabetes type 2, among others, due to genetic disorders, age, lifestyle and wrong diet.

The diagnosis of DM is based on the examination of blood glucose levels. The recommended glucose test is an enzymatic glucose test with venous blood plasma. Blood glucose used for assessment is fasting blood glucose, postprandial and HbA1c 7.

### Table 1: Value of Blood Sugar Examination

<table>
<thead>
<tr>
<th>Fasting blood glucose</th>
<th>Post-prandial blood glucose</th>
<th>HbA1c</th>
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<tr>
<td>Diabetes ≥ 126 mg/dL</td>
<td>≥ 200 mg/dL</td>
<td>≥ 6.5%</td>
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<tr>
<td>Normal &lt;100 mg/dL</td>
<td>&lt; 140 mg/dL</td>
<td>&lt; 5.7%</td>
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Non-Pharmacological Therapy for Type 2 Diabetes Mellitus - Good nutrition or diet is the key to successful diabetes management. The recommended diet is food with a balanced composition of carbohydrates, proteins and fats. The goals of dietary treatment in diabetes are 8: a) Achieve and then maintain near normal blood glucose levels; b) Achieve and maintain near-optimal lipid levels; c) Prevent complications, and d) Improving the quality of life. Nutrition therapy is recommended for all patients with diabetes mellitus; the most important of all nutritional therapy is optimal metabolic results and prevention of complications.

In addition, exercising can lower and maintain normal blood sugar levels. With the principle that there is no need for heavy exercise, a light exercise done regularly will ideally affect health. Some examples of recommended sports include walking or jogging, cycling, swimming, etc. Exercise will increase the use of glucose so that glucose levels in the body fall and remain normal.

Pharmacological Therapy of Type 2 Diabetes Mellitus - The main goal in managing diabetes mellitus is to normalize or regulate insulin activity and blood glucose levels to reduce the occurrence of complications. Drugs used to treat diabetes are usually in the form of oral drugs other than insulin injection. Its use is adapted to the clinical situation of diabetic patients 9.

There is a possibility of Primary failure, and Secondary failure in the therapy carried out. Primary failure is a condition where the dose (starting from the lowest) given is considered ineffective so that the dose is started to be increased until it reaches the effective dose for the patient. If it remains ineffective until the highest or maximum administration dose, then secondary failure occurs in the patient. Secondary failure is a condition where failure occurs with the highest dose of therapy, so it is necessary to change the drugs used and even combine drugs. Combinations of drugs are also performed on complications.

Sulfonylureas-Drugs of this class have the main effect of stimulating insulin secretion by the beta cells of Langerhans in the pancreas. This drug is no longer helpful in people with diabetes with Langerhans beta-cell damage. Weight gain and hypoglycemia are the main side effects of sulfonylurea stimulation of Langerhans beta cells 10. The pharmacodynamics of sulfonylureas begins with binding and blocking ATP sensitive potassium ion (K+) channels. This reduced K+ condition causes membrane depolarization so that calcium ion (Ca+) channels open and Ca+ enters from the outside and releases insulin. The intestine absorbs sulfonylurea derivatives well. After absorption, the drug is dispersed throughout the extracellular fluid. Some sulfonylureas are bound to plasma proteins in plasma, mainly albumin (70%-90%). Pharmacokinetics that occur are different in each sulfonylurea preparation 11.

### Table 2: Pharmacokinetics of the Sulfonylureas

<table>
<thead>
<tr>
<th>Description</th>
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<tbody>
<tr>
<td>Tolbutamide</td>
</tr>
<tr>
<td>Chlorpropamide</td>
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<tr>
<td>Glipizide</td>
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<tr>
<td>Glibenclamide</td>
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Gludin-This class of drugs has the same action as the sulfonylureas, which stimulates Langerhans beta cells in the pancreas to secrete insulin. This group stimulates insulin by closing ATP-independent K channels in pancreatic beta cells. Repaglinide and nateglinide are 2 types of glinide drugs. With oral administration, absorption is rapid, and peak levels are reached within 1 hour. Its half-life is 1 hour, so it should be given several times a day, before meals. The central metabolism occurs in the liver, and the metabolites are inactive. About 10% is metabolized in the kidneys. Patients with impaired liver or kidney function should be given with caution. The main side effects are hypoglycemia and gastrointestinal disturbances 12.
Biginides—This group of Biguanides has the effect of lowering blood glucose levels in people with diabetes and increasing the sensitivity of cells to insulin. This decrease in blood glucose levels is caused by an increase in glucose intake into muscles, a decrease in increased gluconeogenesis and an inhibition of glucose absorption in tissues. Metformin is the only biguanide available. Metformin is the drug of the first choice in overweight patients in whom a strict diet fails to control diabetes. Metformin reaches peak blood levels after 2 hours and is excreted in the urine intact with a half-life of 2-5 hours. Metformin is eliminated by renal tubular secretion and glomerular filtration. This drug does not cause hypoglycemia in non-diabetic patients unless excessive doses are given, and the metformin can cause lactic acidosis in patients with impaired renal function. Therefore, it should not be given even to patients with mild renal impairment.

Thiazolidinediones (rosiglitazone and pioglitazone) bind to peroxisome proliferator-activated receptor gamma (PPARγ), a nuclear receptor in muscle and fat cells. This group has the effect of reducing insulin resistance by increasing the amount of glucose transporting protein, thereby increasing peripheral glucose uptake. Drugs belonging to this group are Pioglitazone. Thiazolidinediones are contraindicated in patients with heart failure because they can exacerbate oedema/ fluid retention and impair liver function (periodic monitoring is necessary).

Alpha-glucosidase inhibitors—These drugs work competitively to inhibit the action of alpha-glucosidase enzymes in the digestive tract so that they can reduce postprandial hyperglycemia. Drugs belonging to this group are Acarbose and Miglitol. The onset of action of Acarbose is 0.5 hours, half-life 1-2 hours, duration 4 hours. The onset of action of Miglitol is 2-3 hours with a half-life of 3 hours. Alpha-glucosidase inhibitors have a mechanism of action by inhibiting the action of the alpha-glucosidase enzyme found on the “brush border” on the surface of the small intestine membrane. Alpha-glucosidase enzymes function as enzymes that break down carbohydrates into glucose in the small intestine. With the administration of alpha-glucosidase inhibitors, the hydrolyzed oligosaccharides will be reduced so that the breakdown and absorption of carbohydrates in the intestine will be reduced, and blood glucose levels will automatically decrease. Insulin levels are not affected because it acts on the intestine.

DPP-IV Inhibitors—This Dipeptidyl Peptidase-IV (DPP-IV) inhibitor class inhibits the action of the DPP-IV enzyme so that glucose-like peptide-1 (GLP-1) remains in high concentration and active form. GLP-1 is an enzyme that can powerfully stimulate the release of insulin and inhibit glucagon secretion. Drugs belonging to this group are Sitagliptin and Linagliptin.

SGLT-2 Inhibitors—SGLT 2 inhibitors work by lowering glucose by blocking glucose reabsorption in the proximal renal tubule. This medicine can reduce weight and blood pressure. Examples are Canagliflozin, Dapagliflozin, Empagliflozin. This drug increases glucosuria. Possible side effects are genitourinary infection, polyuria, hypotension, dizziness, elevated LDL-C and transient creatinine elevation.

Combination Oral Antidiabetic Drugs—Combination therapy with oral antidiabetic drugs is given in the event of secondary failure of these drugs. This combination therapy, either separately or fixed-dose combination, must use two drugs with different mechanisms of action. Diabetes mellitus is a disease that can cause various kinds of complications.

RESULT AND DISCUSSION

This study is an ex post facto or retrospective comparative causal study by looking at the average difference in blood sugar reduction in 2 groups of subjects to determine whether there is a significant effectiveness comparison between a single oral antidiabetic drug and a combination oral antidiabetic drug in lowering blood sugar. The number of samples in this study was 30 patients, namely 15 patients using a single oral antidiabetic drug and 15 patients using a combination oral antidiabetic drug.

Table 3: Average (Mean) Blood Sugar Value Based on Drug Type

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Mean</th>
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<tbody>
<tr>
<td>Check Blood Sugar 1</td>
<td>228.47</td>
</tr>
<tr>
<td>Check Blood Sugar 2</td>
<td>294.07</td>
</tr>
<tr>
<td>Check Blood Sugar 3</td>
<td>137.00</td>
</tr>
</tbody>
</table>

The table above show that the average decrease in blood sugar from the first day to the third day appears to be decreasing. The table also shows that the average decrease in blood sugar ratio in patients taking a single antidiabetic drug was not significantly different from the average decrease in patients using a combination antidiabetic drug.
This test was conducted to determine whether there was a significant difference in reducing blood sugar in the use of 2 types of drugs. The T-Test will get the p-value (sig.) for each variable. It is stated that there is a significant difference when getting \( P < 0.050 \).

The table above shows a significant reduction in the comparison between a single oral antidiabetic drug and a combination antidiabetic drug on the first day.

The tables and graphs in the Univariate analysis show that the average blood sugar value decreased from the first day to the third day. Graph 1 shows that the average decrease in blood sugar between a single antidiabetic and a combination antidiabetic is not proportional.

The table in the Bivariate analysis shows a significant difference between the use of oral antidiabetic drugs with a single on the first day of blood sugar checks. Most of the patients taking combination antidiabetic drugs have higher blood sugar than patients taking single antidiabetic drugs.

Many factors inhibit or interfere with the work of a drug, one of which is age. In patients who are elderly (elderly), physiological functions (such as organs) decrease so that the absorption process of the drug takes longer. The patient's co-morbidities also affect the work of drug metabolism. The results of drug metabolism that can be maximally absorbed are reduced because there are disturbances in the organs in charge of absorbing them, such as the liver, kidneys and intestinal (intestines) organs. In addition, the work of antidiabetic drugs is not optimal; it can be caused by the use of other drugs whose effects reduce the effectiveness of antidiabetic drugs. Hereditary or genetically acquired factors can also affect the action of a drug. Genetic makeup can influence drug biotransformation. This factor determines whether there are naturally occurring enzymes capable of breaking down drugs. There are interactions between drugs and other drugs that give more effect by supporting each other (synergistic reactions) and some that inhibit each other (antagonistic reactions).

CONCLUSION

Antidiabetic drugs can lower a patient's blood sugar, either used alone or in combination. The study results obtained by using medical record data from patients with type 2 diabetes mellitus who were hospitalized showed that there was no significant effectiveness comparison between single antidiabetic drugs and the combination used by the patients. Thus, to better adjust the use of antidiabetic drugs in terms of quantity, medication and duration of treatment with the patient's health condition. Increase education to patients to continue taking drugs and maintain a good lifestyle after being discharged from the hospital. In addition, it is necessary to improve data completeness, information writing and clarity in writing data in medical records so that researchers can easily read them and get complete data.

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